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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,278	11/05/2001	Sydney David Finkelstein	FINKEL-1 CONT II	2727

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,278	FINKELSTEIN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/7/04; 9/13/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 7, 2004 and September 13, 2004. Currently, claims 18-45 are pending.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 7, 2004 has been entered.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection necessitated by amendment.

Priority

5. This application claims priority to 08/667,493, filed June 24, 1996 and 08/311,553, filed September 23, 1994.

Drawings

6. The drawings are acceptable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 18-36, 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Ezra et al. (J. of Histochemistry and Cytochemistry, Vol. 39, No. 3, pages 351-354, 1991) in view of Shibata et al. (Am. J. of Pathology, Vol. 121, No. 3, pages 539-543, September 1992) and McKenzie et al. (US Pat. 5,491,062, February 1996).

Ben-Ezra et al. (herein referred to as Ben-Ezra) teaches analyzing the effect of fixation on the amplification of nucleic acids from paraffin-embedded material by PCR. Ben-Ezra teaches that amplification of nucleic acids from paraffin-embedded material by PCR is increasingly being used to detect viral genomes and oncogene mutations. Ben-Ezra teaches analyzing two surgical pathology specimens, one a fibrocystic disease of breast and the other a fibroadenoma of the breast. Ben-Ezra teaches taking a single 6 um section after fixation and paraffin embedding and placing the section in a

polypropylene tube (limitations of Claim 19, 20). The tissue was deparaffinized and allowed to dry. Ben-Ezra also teaches that the deparaffinized material may be subjected to Proteinase K digestion with or without phenol/chloroform extraction before use in PCR reactions (page 353, col. 1). Ben-Ezra teaches 50ml of water was added to each tube and the tissue was boiled for 10 min. Ben-Ezra teaches that 45ml of this boiled extract was used in a 100ul PCR reaction. Ben-Ezra teaches PCR cycling between 95C and 55C. Ben-Ezra teaches that the products of the PCR reaction were size fractionated and hybridized for analysis (page 352, col. 1). The PCR studies were performed in duplicate (limitations of Claim 36).

Ben-Ezra does not specifically teach analyzing a biological specimen under a microscope to select a target based upon histopathologic characteristics and placing the targeted cells on a slide. Moreover Ben-Ezra does not specifically teach a set of centrifugation following the boiling extraction to obtain a DNA containing supernatant and cycling the PCR reaction for 5 minutes.

However, Shibata et al. (herein referred to as Shibata) teaches a method of specific genetic analysis of microscopic tissue after selective ultraviolet radiation fraction and the polymerase chain reaction. Shibata teaches that the DNA extracted from tissues consists of a variable mixture of stromal, inflammatory, and parenchymal cells. Shibata teaches that this heterogeneity can obscure the location or the detection of genetic aberrations if only a minority of target cells are present. Shibata teaches that target cells can be separated from contaminating background cells by physically isolating histologically defined regions of frozen and fixed tissues. Shibata teaches a

method of placing a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically, Shibata teaches using stained sections of tissues which are approximately 0.1 cm thick (limitations of Claim 18 a b, 19). Under the microscope, cells were selected and placed in a tube (limitations of Claim 21). The slide was separated and placed into microfuge tubes (limitations of Claim 22). For studies of p53 gene expression/mutations only 3x3 mm areas surrounding the dotted areas were placed in microfuge tubes (i.e. a piece of the sample is separated, having a size essentially .5cm or less, from the specimen with the target part of the piece)(limitations of Claim 18d). DNA was then extracted and the boiled (limitations of Claim 18e, 24). The extraction solution comprises a lysis buffer of 100 mmol/l Tris-HCL, 2 mmol/l ethylene diamine tetraacetic acid and proteinase K (limitations of Claim 24-25). Upon extraction, PCR assays were used to detect several targets (limitations of Claim 18f). PCR products were analyzed with two specific oligomers to distinguish between the two alleles on two filters (limitations of Claim 28-30, 36). Tissue sections were examined for the loss of herterozygosity of p53 and the technique was demonstrated to be effective in detecting LOH in the small number of target cells selected as being neoplastic in contrast to cells that were selected as being non-neoplastic (limitations of Claim 18g, 31-32).

Moreover, McKenzie teaches that in a method of boiling extraction of genomic DNA from cells, the cells are placed in a tube and centrifuged. The tubes were placed into a boiling water bath for 15 minutes, after which time they were momentarily centrifuged to pellet the cellular debris. The unpelleted crude lysate was diluted with UV-irradiated water to appropriate concentrations and added directly to the PCR reaction. McKenzie thus teaches centrifuging the aqueous solution from the extraction and creating a pellet and a DNA-containing supernatant and using the supernatant for the PCR reaction. McKenzie teaches the supernatant that is placed in the PCR reaction is a cycle at 92CF for 5 minutes and 55C (col. 9)(limitations of Claim 33).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the DNA extraction and analysis method of Ben-Ezra who teaches a method of boiling for extraction from tissue samples with the teachings of Shibata who specifically dissects the target of interest and places the cells in a tube and the teachings of McKenzie who momentarily centrifuges the boiled extract to pellet the cellular debris. The ordinary artisan would have been motivated to have specifically selected a section of the tissues that contained the target of interest from the tissue such that the cells were histopathologically abnormal, as taught by Shibata (page 539, col 1-2). By selecting a section with histopathologically abnormal cells from the specimens, the ordinary artisan would reduce the background of normal cells within the extract and would be able to more specifically detect abnormalities within the sequences. The ordinary artisan would further recognize that by sampling tissues that appeared abnormal or cancerous, for example, would allow for the analysis of the

genetic basis for the abnormality. By reducing the heterogeneity of the sample by selecting sections which show abnormality, the ordinary artisan would obtain a sample which contains a lower concentration of normal cells. Thus, there would be significant benefits for specifically targeting the tissues as taught by Shibata. Moreover, while Ben-Ezra teaches boiling the sample for extraction, Ben-Ezra does not explicitly teach centrifuging the sample to create a pellet and a DNA-containing supernatant. However, McKenzie specifically teaches a boiling method that, like most boiling methods, provides for a momentary centrifugation to pellet the cellular debris. The ordinary artisan would have been motivated to have pelleted the cellular debris to remove the debris prior to performing a sensitive PCR reaction. Without performing the brief centrifugation, the PCR reaction would contain much cellular debris and other material which is unnecessary and harmful to the PCR reaction. Therefore, at the time the invention was made, the ordinary artisan would have been motivated to have specifically targeted particular specimens for the reasons provided by Shibata and pelleted the cellular debris as taught by McKenzie to obtain the invention as a whole.

With respect to Claim 33, Ben-Ezra teaches PCR cycling between 95C and 55C, however does not specifically teach a cycle for 5 minutes. However, McKenzie teaches a PCR program which has cycling at 92C for 5 minutes and 55C. The ordinary artisan would have recognized that there are many different PCR conditions which will result in equivalent results. The ordinary artisan would have been motivated to have performed any one of these cycling techniques including the cycling of McKenzie.

With respect to Claims 42-45, the claims are directed to diagnosing inherited disease, infectious disease and genetic polymorphisms in a patient. Ben-Ezra teaches that the method may be used for detecting the presence of viruses, or of oncogene mutations. Upon detection of a virus, an appropriate treatment would be advisable. Shitbata further teaches that the methods for detection of loss of herterozygosity in p53 which is an inherited disease. Shibata specifically teaches using two allelic specific oligonucleotides.

9. Claims 37-41are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Ezra et al. (J. of Histochemistry and Cytochemistry, Vol. 39, No. 3, pages 351-354, 1991) in view of Shibata et al. (Am. J. of Pathology, Vol. 121, No. 3, pages 539-543, September 1992) and McKenzie et al. (US Pat. 5,491,062, February 1996) as applied to Claims 18-36, 42-45 above and further in view of Perlin (US Pat. 5,5580,728, December 1996).

Neither Ben-Ezra, Shibata, or McKenzie specifically teach using a database for analyzing the results of genotyping.

However, Perlin teaches a method and system for genotyping which comprises a computer and a database. Pelrin teaches that using the computer allows for a fully automated method for accurately determining alleles. Perlin teaches that signal may be detect by means of a computational deice and then determining the genotype of the location of the DNA. Perlin teaches that standard PCR amplification is used (col. 9, lines 10-20). Perlin teaches that assaying the amplified material is based on size and

concentration. The gels image is put into machine readable digital format by electronic scanning of a gel image by phosphor image or fluorescence-base, for example (col. 11, lines 15-30). This can also be performed by hybridization of nucleic acid probes with the amplified material or by any other physical means for detecting relative concentrations of nucleic acid species (col. 11, lines 40-50). Perlin provides many formulas for analyzing the data. The system comprises a computer, with inputting means, memory and outputting means (col. 20, lines 60-65). Perlin teaches the method may be used with respect to phenotypic risk of disease for the individual, genetic linkage maps, genome maps, cloning a disease gene, treating disease, monitoring cancerous materials, fingerprinting, performing population genotyping studies, and assessing genetic risk.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the genotyping method of Ben-Ezra, Shibata, and McKenzie to include a computer/database as taught by Perlin. Perlin specifically teaches the benefit and uses of a database such that genotyping methods are fully automated for accurately determining sequences. The ordinary artisan would have recognized the benefits of using a fully automated system for ease and accuracy. Thus, modifying a manual method with an automated system would have been obvious to the skilled artisan at the time the invention was made.

Conclusion

10. No claims allowable over the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
November 22, 2004